

PREGABALIN: THE NEXT NEW THING

Safety and Efficacy of Two Pregabalin Regimens for Add-on Treatment of Partial Epilepsy

Beydoun A, Uthman BM, Kugler AR, Greiner MJ, Knapp LE, Garofalo EA; Pregabalin 1008-009 Study Group

Neurology 2005;64:475–480

OBJECTIVE: To evaluate the efficacy, tolerability, and safety of two pregabalin regimens administered as adjunctive therapy to that of placebo in patients with medically refractory partial epilepsy.

METHODS: A multicenter, double-blind, randomized, parallel-group, placebo-controlled trial was performed. After a prospective 8-week baseline phase, patients were randomized to 12 weeks of double-blind treatment with placebo or pregabalin, 600 mg/day, administered twice daily (BID) or 3 times daily (TID). Primary efficacy was measured as change in seizure frequency from baseline of either pregabalin regimen compared with placebo. Secondary efficacy comparisons included the proportion of patients experiencing $\geq 50\%$ reduction in seizure frequency (responder rate) and median percentage change from baseline in seizure frequency. Safety/tolerability assessments included adverse events (AEs), physical and

neurologic examinations, and clinical laboratory evaluation. Efficacy and safety analyses were performed on the intent-to-treat (ITT) population.

RESULTS: Pregabalin treatment resulted in seizure frequency reductions: 53% for pregabalin TID ($P \leq 0.0001$) and 44% for pregabalin BID ($P \leq 0.0001$) compared with a 1% increase for placebo. Responder rates were 49% for pregabalin TID and 43% for pregabalin BID compared with 9% for placebo ($P \leq 0.001$). Both pregabalin regimens were similar in efficacy and tolerability. The most common AEs were dizziness, somnolence, and ataxia.

CONCLUSIONS: Pregabalin administered at 600 mg/day is safe, generally well tolerated, and efficacious as adjunctive therapy for the treatment of patients with partial seizures, with or without secondary generalizations. This dose can be administered on a twice-daily or 3-times-daily schedule with similar efficacy and tolerability results.

COMMENTARY

In June 2005, pregabalin was approved by the Food and Drug Administration for adjunctive treatment of partial-onset seizures. The article by Beydoun et al. reports the results of one of three pivotal trials performed to evaluate pregabalin for this indication. The other two were dose-ranging trials, which demonstrated that 50 mg/day had no effect, but dosages of 150 mg/day, 300 mg/day, and 600 mg/day all resulted in significant reductions in seizure frequency in comparison to placebo (1,2). Determining efficacy, however, was a secondary objective of the trial of Beydoun et al.; the primary purpose was to compare the effect of a twice-daily (BID) dosage with a 3 times daily (TID) dosage, at the same target dose of 600 mg/day. Efficacy with both regimens was impressive, but proof of the primary hypothesis was less convincing.

Like its predecessor compound, gabapentin, pregabalin inhibits neurotransmitter release by binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels. Although facetiously described

as the “son of gabapentin,” it seems to be considerably more robust than its parent. It is severalfold more potent in animal epilepsy models, and preliminary human data also suggest greater efficacy (1,2). It shares favorable characteristics of gabapentin, such as lack of pharmacokinetic interactions and enzyme induction.

Trial Design and Results

This trial design was a classic one in which pregabalin was added to one to three baseline drugs in a parallel comparison with placebo. However, the connoisseur of clinical trials will note some subtle differences in trial design and outcome. One third of patients were randomized to pregabalin, to 600 mg/day BID, 600 mg/day TID, or to placebo. Dosage escalation was rapid, every 2 days, with the target dose of 600 mg/day reached on day 8. Patients enrolled had quite refractory seizures, with mean seizure frequencies of 21 to 25 a month. Two thirds were taking two or three baseline drugs. These features are relevant to interpretation of efficacy and tolerability results. The usual mindless exclusion of patients taking felbamate occurred, even those taking it uneventfully for many years: serious adverse effects of aplastic anemia or liver failure do not appear after 2 or more years of felbamate therapy. The notorious, although

parametric, R-ratio was used to calculate the primary efficacy measure, but the authors wisely translated these ratios into the more understandable seizure-frequency reduction, expressed by median percentage and 50% responder rates. Efficacy results were outstanding. Although meta-analyses are frowned on by statisticians, plugging these results into the meta-analysis procedure reported by Cramer et al. suggests that this dose of pregabalin compares favorably in terms of responder rates (50% seizure-reduction rates) with optimal dosages tested for topiramate, oxcarbazepine, levetiracetam, and zonisamide (3).

Placebo Response

The very low placebo response in this trial—a 9% responder rate and a 1% increase in median seizure frequency—bears comment. Burneo et al. reported that the placebo 50% responder rate in similar antiepileptic drug trials ranged from 9.6 to 16.6% (4). Statistically, a low placebo response is a virtue, reducing the background noise. However, it could be a clue that the blinding was less than completely effective. These were veteran patients. The common side effects of pregabalin (dizziness, sleepiness, and ataxia) would not be surprising to them. Such a savvy group might be able to discern with some accuracy whether they were taking placebo or the real thing, especially with the high target dose and rapid escalation. The same is true of the investigators and research coordinators. Research personnel, of course, should not convey their opinions to patients about whether they are taking placebo or drug, but in practice, this can happen in subtle ways. Clinicians have been known to reassure patients who do not seem to be responding favorably that they may not be taking the actual drug and to express pleasure at seizure reductions. Both actions are improper during the double-blind period and can affect the results. If patients guess that they are taking active drug, the efficacy outcome might be enhanced. Alternatively, an accurate guess that one is taking a placebo might wipe out much of the placebo response. The common procedure of subtracting the placebo response from the drug response to arrive at an efficacy estimate is therefore not as logical as it sounds. This is another reason to view meta-analyses with caution.

BID or TID?

As stated, the primary purpose of this clinical trial was to compare the efficacy of pregabalin administered BID with pregabalin administered TID at the same target dose. Was this goal achieved? Certainly, both pregabalin dosages were highly effective in comparison with placebo. In that sense, the authors are on solid ground in recommending that a BID schedule be tried initially because this is more convenient and increases compliance. Nevertheless, stating that both regimens were effective

and that no statistical difference in efficacy was found between them is not the same as proving that they are equivalent. The authors state that the study was “not powered to demonstrate equivalence between the two pregabalin treatment regimens.” The TID regimen resulted in a 53% median seizure-frequency reduction compared with 44% for the BID regimen, with similar differences for the responder rates. Not only did the TID regimen result in a greater decrease in median seizure frequency, but it also was correlated with greater reductions at all calculated seizure percentages (i.e., 25%, 50%, 75%, and 100%) than the BID regimen.

A trend exists for manufacturers of antiepilepsy drugs with a short pharmacokinetic serum half-life to minimize the disadvantage of the short half-life by designing clinical trials intended simply to demonstrate that a BID schedule is superior to placebo. The reason for such a trial design is that the pharmacodynamic effect of the drug may extend beyond what the serum half-life would imply. This is biologically possible. However, a simpler reason for the observed superiority of a BID regimen to placebo in a clinical trial is that the BID schedule provides adequate protection during most of the 24-hour period and so is more efficacious than placebo. However, the BID schedule still may provide less than optimal protection at trough. Beydoun et al., therefore, quite correctly point out that “for patients not adequately controlled on a BID schedule at maximally tolerated dosage, a TID regimen may be considered.” Perhaps the same advice should be applied to levetiracetam, oxcarbazepine, tiagabine, and gabapentin.

Efficacy and Tolerability

Pregabalin efficacy for refractory partial epilepsy was convincingly shown in this trial and two others (1,2). Efficacy seems to be considerably better than that of gabapentin for adjunct use. The dropout rates resulting from adverse events were relatively high, 19% for TID and 26% for BID (compared with 7% for placebo) but not unreasonable for this top-end target dose of 600 mg/day. The authors are to be commended not only for listing the adverse events but also for listing the percentage of dropouts caused by each adverse event. This makes it easy to see that dizziness, somnolence, and ataxia accounted for nearly all of the dropouts on drug regimens and no dropouts on placebo. One adverse event that bears watching, as more experience is gained, is weight gain, noted by 15 to 20% of patients taking drug compared with 2% taking placebo. Pregabalin will very likely be a useful addition to our treatment options. This study did not prove that the BID schedule is as good as the TID schedule, but it did demonstrate that BID dosing might be satisfactory for many patients.

by Edward Faught, MD

References

1. French JA, Kugler AR, Robbins JL, et al. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. *Neurology* 2003;60:1274–1283.
2. Arroyo S, Anhut H, Kugler AR, Lee CM, Knapp LE, Garofalo EA, Messmer S; Pregabalin 1008-011 International Study Group. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. *Epilepsia* 2004;45:20–27.
3. Cramer JA, Fisher R, Ben-Menachem E, French J, Mattson RH. New antiepileptic drugs: comparison of key clinical trials. *Epilepsia* 1999;40:590–600.
4. Burneo JG, Montori VM, Faught E. Placebo effect in antiepileptic drug trials. *Epilepsy Behav* 2003;4:371–373.